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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/825,713	04/04/01	DURING M	DUR01-NP001

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EXAMINER	
KATCHERES,K	
ART UNIT	**PAPER NUMBER**
1636	4
DATE MAILED:	08/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/825,713	Applicant(s) DURING ET AL.	
	Examiner Konstantina Katcheves	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 1-19 are pending in the instant application.

Claim Objections

Claim 19 is objected to because of the following informalities: In claim 19, step (e) the word system is misspelled. Appropriate correction is required.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 7, 9, 10-15 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Ourednik et al. (Clin. Genet. Vol.56 1999) (hereinafter "Ourednik") and Kopen et al. (PNAS Vol.96 1999) (hereinafter "Kopen").

The invention of the instant claims is drawn to a method of the delivery of mammalian stem cells into the mammalian nervous system for the treatment of neural disorders. The invention further is drawn to the delivery of stem cells transfected with foreign genes for the purposes of gene therapy. The method includes administering stem cells into a subject mammal, the migrating of the cells into the nervous system and the engrafting of the cells at a preferred site. The method further includes the differentiation of said cells to replace damaged nervous system tissue.

Ourednik discloses the utilization of stem cells to promote the repair of the nervous system by replacing the affected cell population by neural grafts and providing missing neuroactive molecules by expressing exogenous proteins in the transferred cells. Ourednik discloses the transfer of therapeutic genes to the nervous system by altering stem cells genetically *ex vivo* to produce a desired protein. Those cells are then introduced into discrete or widespread reasons of the nervous system. See page 267 and 268. Ourednik further discloses that the stem cells can be stably transfected to express a desired protein, that they are able to migrate and intermingle with host cells and that they are able to differentiate and assume the phenotypes of the regions of engraftment for the treatment of neural disorders in both discrete and widespread locations. See page 269, table 1. Ourednik fails to specifically disclose myeloid stem cells in the practice of the method.

Kopen discloses that stem cells of myeloid origin, i.e. hematopoietic stem cells or marrow stromal cells, can adopt neural cell characteristics when exposed to the brain environment. Limited accessibility of neural stem cells hinders their utility as a treatment vector for diseases of the nervous system. See page 10711, column 1. Kopen demonstrates that these cells mimic the behavior of neural progenitor cells by participating in aspects of neural development including proliferation, migration, integration within regions and differentiation into astrocytes and even neurons. See page 10715.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to deliver myeloid stem cells to the nervous system of a mammal. The ordinary skilled artisan would have been motivated to myeloid cells as disclosed in Kopen because a supply of which is more accessible than the neural cells disclosed in Ourednik. Additionally, the ordinary skilled artisan would reasonably expect myeloid stem cells to be useful in the method disclosed by Ourednik because these cells have been shown to adopt the behavior of neural progenitor cells by participating in aspects of neural development including proliferation, migration, integration and differentiation into neural cells. Thus the ordinary skilled artisan would expect that these cells would be capable of migrating to a preferred site in the nervous system, integrating or engrafting into the nervous system, and differentiating to neuronal cells such that damaged tissue may be treated. Therefore, absent evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim 1-7, 9, 10-15 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ourednik in view of Kopen as applied to claims 1-4, 6, 7, 9, 10-15 and 17-19 above, and

further in view of Eglitis et al. (PNAS Vol.94 1997) (hereinafter "Eglitis"), insofar as the methods are drawn to mouse and rat models.

The invention of the instant claims is relied upon as described above and further comprises the limitation that the myeloid stem cells of the method differentiate into neuronal and glial cells.

Ourednik and Kopen together teach a method wherein myeloid stem cells are delivered to the nervous system of a mammal. Those cells, which are of hematopoietic origin, are capable of differentiation into neural cells according to Kopen.

Eglitis finds that after the transplantation of bone marrow cells into the brains of mice the cells are capable of migration to discrete parts of the brain. Eglitis further shows that bone marrow derived cells acquire microglial antigenic markers and finds hematopoietically derived microglia in the brains of rats.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to deliver myeloid stem cells to the nervous system of a mammal. The ordinary skilled artisan would have been motivated to myeloid cells as disclosed in Kopen because a supply of which is more accessible than the neural cells disclosed in Ourednik. Additionally, the ordinary skilled artisan would reasonably expect myeloid stem cells to be useful in the method disclosed by Ourednik because these cells have been shown to differentiate into neural cells, as disclosed by Kopen, and glial cells, as disclosed by Eglitis. Thus the ordinary skilled artisan would expect that these cells would be capable of migrating to a preferred site in the nervous system, integrating or engrafting into the nervous system, and differentiating to neuronal cells such that damaged tissue may be treated. Therefore, absent evidence to the contrary, the

invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim 1-4 and 7-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ourednik in view of Kopen as applied to claims 1-4, 6, 7, 9, 10-15 and 17-19 above, and further in view of Cheng et al. (Blood Vol.92 1998), insofar as the methods are drawn to mouse and rat models.

The invention is relied upon as described above and further comprising cells expressing CD34 (CD34+).

Ourednik and Kopen are relied upon as described above however the instant references fail to disclose CD34+ cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use myeloid stem cells expressing the CD34 surface antigen in the above method. The ordinary skilled artisan would have been motivated to use cells expression the CD34 antigen because hematopoietic cells are members of the population of cells that bear the CD34 antigen. Myeloid stem cells, cells derived from hematopoietic cells, make attractive targets and vehicles for somatic cell-based gene therapy because they have the ability to continue producing the therapeutic gene indefinitely. Therefore, absent evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections – 35 USC § 112

First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods drawn to mouse and rat models, does not reasonably provide enablement for methods drawn to the treatment of human subjects. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors considered in the rejection of the instant claims may include: the nature of the invention, the state of the prior art and the predictability or unpredictability of the art, the amount of direction or guidance presented in the specification and the presence or absence of working examples, the breadth of the claims and the quantity of experimentation.

Applicant's invention of the instant claims is drawn to a method of the delivery of mammalian stem cells into the mammalian nervous system for the treatment of neural disorders. The invention further is drawn to the delivery of stem cells transfected with foreign genes for the purposes of gene therapy. Although the specification discloses the delivery of myeloid stem cells to the nervous system of Parkinsonian rats and mice, there is no indication that the methods would necessarily work in humans.

Applicant's specification shows the method practiced with Parkinsonian rats and mice where these models had neurons lesioned with the neurotoxin 6-OHDA-HBr. The specification provides no indication the models used would necessarily indicate that the method of delivery would be effective in humans nor does the specification provide for the treatment of human

neurological disorders. Although very promising for ultimate human CNS therapy, these findings need first to be reproduced in animals that are closer to humans. Maritenez-Serrano et al. (TINS Vol.20 no.20 1997) (hereinafter "Martinez") recognizes the possible clinical applications of stem cells the therapy of CNS disease yet addresses the obstacles in treating CNS disease with *ex vivo* gene therapy of cells. Martinez states that research "is still in its infancy, and our knowledge of the biological mechanisms regulating maturation and differentiation of multipotent neural progenitors remains highly incomplete." Martinez illustrates the difficulties of obtaining stable, long-term function expression of genes *in vivo* and expressly states that "further improvement in gene transfer procedures is needed." New vector systems must be developed that will achieve cells with sustained high-level expression that also functions well in the *in vivo* brain environment. Furthermore, Martinez states that it is also necessary to "explore efficient regulatable expression systems and safety mechanisms which will make it possible to modulate or switch off the production of a transferred protein, or even eliminate the cells themselves if necessary.

Upon examination of Applicant's disclosure, the evidence or data provides no indication that the method of delivery of myeloid stem cells or that the method of treating disease comprising the delivery of myeloid stem cells would work in subjects other than mice and rats. Without further evidence, Applicant has not overcome the state of the art in his specification and is not enabled for methods of delivering myeloid stem cells in humans or treating neurological disease in human subjects. Considering the inherent difficulties in the art, Applicant's disclosure does not teach how to overcome those obstacles such that the invention will do what Applicant asserts it will do.

Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 1 recites an incomplete process. Claim 1 is drawn to a method of targeted delivery of mammalian stem cells. However the claim fails to show how the steps result in the targeted delivery of the cells. There is no causal link between the final step of the method which is the engrafting of the cells and the preamble which is drawn to the targeted delivery of cells.

Claims 2 and 11 are vague and indefinite as to the metes and bounds of the claim because they claim mammalian cells "derived from" bone marrow, peripheral blood, umbilical cord blood, or fetal liver tissue. "Derived" is a term that is non-specific and relative in nature for which Applicant provides no definition. It provides no clarity as to what Applicant's claimed invention includes and what it does not include. Without a more specific definition of the claim, it is impossible to determine what and how many derivations comprise the invention of derived mammalian cells of myeloid origin. The nature and number of the derivations to arrive at the invention Applicant seeks to protect with the patent are not established such that a person skilled in the art may replicate the invention without undue experimentation. Applicant's disclosure

does not provide any definition as to the process of deriving these cells of the claims nor what is included in the definition of these cells.

The instant claims recite the limitation that the claimed method comprises administering a "therapeutic amount" of mammalian stem cells of myeloid origin. Without clarification, the term, "therapeutic amount," remains unclear. Therapeutic amounts rely on variable factors such as the toxicity of the composition administered, the efficacy of the drug, the type of subject, the weight, size and age of subject, the means of administration, *etc.* The specification does not define a therapeutic amount. Specific guidance is required either in the claim, itself, or the specification in order to particularly point out and distinctly claim Applicant's invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
August 22, 2001

SEAN McGARRY
PRIMARY EXAMINER

ARRY
AMINER